REMARKS

Claims

Claims 10, 12, 13, 21 and 22 are currently under examination pursuant to the restriction requirement mailed June 27, 2008.

Claims 1–9, 14–17 and 23 are hereby withdrawn from consideration pursuant to the aforementioned restriction/election.

Claims 11 and 18–20 were previously cancelled without prejudice or disclaimer.

Claim 24 is added by this paper.

Claim amendments

The claims have been amended as per the Examiner's suggestion. See for example, page 4, 3rd complete paragraph of the outstanding Office Action.

New claim recites each individual polypeptide species of the instant application. The dependency of claims 9, 10, 12–14 and 22–22 has been amended to depend on new claim 24. No new matter is added. Entry thereof is earnestly solicited.

Claim objections

The Examiner is thanked for her careful reading of the claims. The objection of claims 10 and 11 is moot in view of the amendment of the claims.

Rejections under 35 U.S.C. §112, ¶1

The Examiner concedes that the claimed polypeptides are adequately described and enabled by the disclosure in the present specification. See items 8 and 9 of the outstanding Office Action. Accordingly, the foregoing amendments render the rejection of claims 10, 12–13, 21 and 22 under this section moot. Applicants' amendment of the claims should not be construed as acquiescence to this or any other ground of rejection. Withdrawal of the rejection is respectfully requested.

Rejection under §102(b)

The claims of the instant application stand rejected under 102(b), or alternately under §103(a) as allegedly unpatentable over Gavrovic (*Allergy*, 1998), as evidenced by the disclosure in the present specification at page 4, lines 1–22. The Office Action alleges that the specification at page 4

teaches that Sec c4 is the allergen isolated from *Secale cereale* having the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The Office Action further reasons that Gavrovic teaches the same isolated allergen from the same source, so the resulting allergen must necessarily have the sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The Office Action further reasons that since the PTO does not have adequate facilities to check for sequences, the burden falls on the Applicant to show that the molecules of the prior art are different from what is claimed.

Gavorovic fails to teach *Secale cereale c* 4 allergens of the present application and fragments thereof

Applicants have reviewed the structural information of the instantly claimed molecules which range from ~520 amino acids for the complete allergens and ~497 amino acids for the claimed fragments. Applicants have performed *apriori* calculation of the molecular weight (MW) and isoelectric points (pI) of the polypeptides using Compute pI/MW, a program freely available from the Expert Protein Analysis System (EXPASY). The results of the computation are presented in the table below. It should be noted that all the N-terminal signal processed polypeptides of the instant invention, as recited in instant claim 24, are structurally different from Gavorovic's *Secale cereale* allergen. For example, with respect to the processed fragment of SEQ ID NO: 2 recited in claim 11, Compute pI/MW predicts that the theoretical value for the sequence (496 amino acids) is a pI of 9.10 and a MW of 54931.15 daltons. Both values are outside of what is taught by Gavrovic (i.e., MW of 55–60 kDa and pI of 9.2–9.7). As such, the polypeptides recited in (b), (d), (f), (h), and (j) of claim 24 are novel over what is taught by Gavorovic.

Polypeptide	Begins at	Ends at	Length/a.a.	pI	MW/daltons
SEQ ID NO: 2 fragment	23	518	496 a.a.	9.10	54,931.15
SEQ ID NO: 4 fragment	23	520	498 a.a.	9.29	54,904.31
SEQ ID NO: 6 fragment	23	518	498 a.a.	9.29	54,904.31
SEQ ID NO: 8 fragment	22	518	497 a.a.	9.30	54,903.32
SEQ ID NO: 10 fragment	22	518	497 a.a.	8.89	55,237.54

As for the mature polypeptide sequences, which are recited in claim 24, the output of compute pI/MW is provided in the table below:

Polypeptide	Begins at	Ends at	Length/a.a	pI	MW/daltons
SEQ ID NO: 2	1	518	518 a.a.	9.08	57,172.80

SEQ ID NO: 4	1	520	520 a.a.	9.28	57,171.06
SEQ ID NO: 6	1	518	518 a.a.	9.28	57067.93
SEQ ID NO: 8	1	518	518 a.a.	8.89	57496.23
SEQ ID NO: 10	1	518	518 a.a.	8.89	57377.93

Applicants submit that at least the mature polypeptides having the sequence set forth in SEQ ID NO: 2, 8, and 10 have different physiochemical characteristics from Gavorovic's polypeptides. This is because the iso-electric (pI) value of each of the aforementioned mature proteins, which is dependent on the amino acid composition of the polypeptide chain, is different from what is taught by the cited reference. Accordingly, the mature proteins recited in claim 24 (a), 24 (g) and 24 (i) are novel over Gavorovic's disclosure. Withdrawal of the rejection is respectfully requested.

With respect to the *Secale cereale* c 4 allergen of SEQ ID NO: 4 [see claim 24 (c)], Applicants submit that the PTO has not established that Gavorovic's polypeptides are structurally and/or functionally identical to the polypeptide(s) claimed herein. Absent such, the reference cannot anticipate what is claimed herein. For example, posted below are results of the search report carried out on June 16, 2008, which was used in the non-final rejection mailed November 28, 2008. The top ten matching sequences are displayed:

SUMMARIES

Result No.	Score	Query Match	Length	DB	ID	Description
1	1603	100.0	1603	16	AEB28051	Aeb28051 Secale ce
2	1454	90.7	1603	16	AEB28059	Aeb28059 Triticum
3	1431.6	89.3	1603	16	AEB28057	Aeb28057 Triticum
4	1358.8	84.8	1608	16	AEB28055	Aeb28055 Hordeum v
5	1302.4	81.2	1644	16	AEB28053	Aeb28053 Secale ce
6	1119	69.8	1503	12	ADI44453	Adi44453 P. praten
7	1119	69.8	1503	12	ADI44449	Adi44449 P. praten
8	1119	69.8	1503	16	AEB13459	Aeb13459 Phleum pr
9	1119	69.8	1503	16	AEB28061	Aeb28061 Phleum pr
10	1115.8	69.6	1503	12	ADI44451	Adi44451 P. praten

In the analysis which follows the aforementioned table, it is further acknowledged that among these top-matching sequences, *only* AEB28051 (GenBank accession: AJ862830; GI:55859453; which encodes a protein of 518 amino acids) is identical to the instantly claimed polynucleotide of SEQ ID NO: 1. A second *Secale cerale* polynucleotide having ID AEB28053 (GI: 55859455; result 5) exhibited 81.2% identity to the claimed polynucleotide of SEQ ID NO: 1. A

search on NCBI database with the GI accession numbers indicates that the reference sequences encode proteins having GenBank accession Nos. CAH92627 and CAH92630, respectively (see enclosed printouts). The PTO search report further indicates that the reference polynucleotides are disclosed in WO2005-059136 to Feibig et al. Coincidentally, WO 2005-058936 is the WIPO publication of the international application PCT/EP04/13664 (PCT '664) and the present application is the US national phase of PCT '664. None of the other polynucleotide sequences that appear on the search report encode the claimed *Secale cereale c* 4 allergens. To this end, the next top-matching sequence of AEB28059 (GenBank accession: AJ862833; GI:55859459; 90.7% identical to Applicants' polynucleotide of SEQ ID NO: 1) encodes a protein of 518 amino acids (GenBank accession CAH92633). The sequence identity between the Applicants' *Sec c* 4 protein of SEQ ID NO: 2 and the CAH92633 sequence (protein encoded by the DNA identified as result No. 2) at the protein level is 92% (39 mismatches). Similarly, the sequence identity between the Applicants' *Sec c* 4 protein of SEQ ID NO: 4 and the CAH92633 sequence at the protein level is 88% (60 mismatches). See the enclosed BLAST alignment results. Thus it is clear, at least based on the enclosed analysis, that the claimed *Secale cereale c* 4 polypeptides are both novel and unobvious over the art-known proteins.

It is by now well-established that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See MPEP §2131 and further corroborated by the Fed. Circuit's decision in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). With respect to inherency, the Courts have established that "the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Inasmuch as the cited Govorovic says nothing about *Secale cereale c* 4 polypeptide sequences and the Examiner has not established that the Sec c 4 polypeptide disclosed therein necessarily comprises the sequences recited herein, the rejection is without legal merit.

Applicants further submit that for anticipation, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The Office Action fails to establish that the polypeptides

disclosed in the aforementioned reference contain the **complete** Sec c4 polypeptide sequence as presently claimed. To this end, Applicants find that a search of the term "Secale cereale sec c 4" in NCBI's protein database results in the identification of at least two Sec c 4 variants (accession Nos. CAH92630 and CAH92627) and an unrelated PEP carboxylase protein (accession No. AAS88378). It cannot be ascertained whether the reference teaches a sequence that is completely different from what is claimed in the present application. More importantly, it is clear that the cited reference of Gavorovic fails to provide "a complete detail" (i.e., the polypeptide sequence) of the claimed invention. As such, an inherency rejection under §102/§103 is not supported and should be withdrawn. See MPEP §2112.

Withdrawal of the rejection is respectfully requested.

Reference fails to teach allergens from *Hordeum vulgare* and *Triticum aestivum*

The rejection is based on the references' disclosure of allergens from *Secale cereale*. Gavorovic is absolutely silent about the Hor v 4 and Tri a 4 polypeptides of the instant invention. Applicants' specification teaches that the proteins of SEQ ID NOs: 6, 8, and 10 represent allergens from *Hordeum vulgare* and *Triticum aestivum*. See paragraph [0013] of the published specification. Insofar as the cited reference is totally silent with regard to allergens from the disclosed species, the polypeptides of claim 24(e), 24(g) and 24(i) are novel over Gavorovic et al. Withdrawal of the rejection is respectfully requested.

Rejection under §103(a)

Claims 10 and 12–13 are rejected under this section as allegedly unpatentable over aforementioned Gavorovic in view of WO 2004/000881. This rejection is respectfully traversed.

The present application claims priority to German priority document No. DE 103 59 351.9 (filed: December 16, 2003), a certified copy of which was furnished with the original application papers and received by the USPTO on June 15, 2006. A certified English translation of the priority document is enclosed with Applicants' previous reply. The disclosure in the priority document supports the present claims. As such, Fiebig (WO 2004/000881; published: December 31, 2003) is not a valid prior art reference under §102(a). It is further noted in this context that even if the rejection were based on the disclosure in the corresponding US publication No. 2006-01774470 (filed: June 11, 2003), *any* holding of obviousness based on Gavorovic's generic

disclosure of *Sec c 4* proteins is scientifically and legally misplaced. See *supra*.

Withdrawal of the rejection is respectfully requested.

Non-obviousness

A combination of the aforementioned Gavorovic and Fiebig also fails to render obvious the claimed subject matter.

An embodiment of the present invention pertains to the preparation of recombinant Sec c 4, Hor v 4 and Tri a 4 allergens (collectively termed group 4 allergens) and hypoallergenic variants and fragments thereof for therapy and diagnostics. The advantages of recombinant proteins over proteins extracted and purified from natural sources are the much higher purity, cheaper preparation and a higher yield and a stable production of a defined protein instead of a mixture of several isoforms and contaminations with other proteins and compounds, leading to a higher yield. Although several peptide fragments of group 4 grass pollen allergens were known since a long time (see, pages 2–4 of the specification), the sequences of these allergens were not elucidated and such sequences were not available at the time the present application was filed. Obviously the previous attempts were not successful because the N-terminal amino acid sequence could not be determined.

The previously failed attempts of other scientists to determine the sequence are described in the chapter "background of the invention," their own work and results are disclosed in the chapter "description of the invention." The sequencing of the first 69 amino acids (N-terminus of the allergen) presented an unforeseeable problem. This part of the protein was not accessible to DNA sequencing and had to determined directly and the respective DNA sequence was deduced from this amino acid sequence leading to the "hybrid" sequences 1, 3 and 5 (see specification and the notes to SEQ ID NOs: 1, 3 and 5 in the sequence protocol). The cloning strategy and method is described in detail in Nandy et al. (BBRC, 2005) and the attached posters (see attachments). These documents show that the performed cloning strategy and method was new and inventive and it was not obvious for a person skilled in the art that this method would lead to a successful cloning of the Group 4 allergens. This was a new and inventive approach that was not disclosed or suggested by the state of the art. A further evidence for the presence of an inventive step is he fact that elucidation of the coding DNA sequence of group 4 allergens was tried intensively but not successful since the end of the 80s by several scientific groups. Many peptide fragments published are the results of such trials. These fragments neither lead to the elucidation of the DNA or amino

acid sequence of group 4 allergens. No scientist would be satisfied with the publication fragments if the full-length sequence would be obtainable by standard technology. Even in 2003, Andersson and Lindholm (Int. Arch. Allergy Immunology, 2003) acknowledge in their review article (see attachments, page 92, right column) that "despite considerable efforts, cloning of a group 4 grass pollen allergen has so far not been reported."

The standard methods being used by a person skilled in the art, like the use of degenerated primers based on the N-terminal peptide sequence, did not lead to the successful cloning of Group 4 allergens, even when repeated several times. Obviously, the other scientific groups also tried such standard techniques and were not successful. Thus, the group 4 allergen sequences claimed herein were not determined and published before the priority date of the present application. Therefore, the cited documents do not give a single hint and do not lead to or teach the inventive cloning strategy or recombinant allergens. The inventive DNA sequence of Sec c 4, Hor v 4 and Tri a 4 presents the first DNA sequence of group 4 allergens ever. Before the elucidation of these DNA sequences and the availability of recombinant group 4 allergens, the claimed polypeptides had to be isolated from natural sources with all the disadvantages described above. Using the methods of the present invention, it can be produced recombinantly in large amounts and in a simple way.

Furthermore, the claimed polypeptides clearly differ from allergens purified from natural sources as there are clear structural differences between protein allergens isolated from natural sources and isolated recombinant allergens. Recombinantly prepared proteins have several advantages over protein preparations which are obtained by extraction and purification from natural sources. Recombinant proteins have a much higher purity with respect to the target protein than protein preparations obtained by extraction and purification from natural sources. The impurity of allergen preparations obtained by extraction and purification from natural sources is for example disclosed in Hoffman on page 602, table 1 (*J Allergy Clin. Immunol.* 75(5):599-605, 1985). Therein, cross-contaminations by other allergens and contaminations by faecal and proteolytic compounds were shown. These contaminations are very critical for the stability and safety of the product and therefore for its potential use in therapy and diagnosis. This difference in purity is a clear structural difference between protein allergens isolated from natural sources and isolated recombinant allergens. Besides the impurity also the low yield is a critical issue for allergen preparations received by extraction and purification form natural sources. As such the polypeptides claimed herein are inventive over the generic prior art teachings.

Favorable reconsideration is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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